AstraZeneca

November 2, 1999

Dockets Management Branch (HFA- 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. 99 – 23009
Comments on Draft Guidance for Industry: "BA and BE Studies for Orally Administered Drug Products – General Considerations"

Dear Madam/Sir:

Reference is made to FDA's draft guidance as described above which was published in the September 3, 1999 Federal Register.

AstraZeneca LP has reviewed this guidance and our comments are attached.

If you have any questions regarding these comments, please do not hesitate to contact me. Thank you for your consideration.

Sincerely,

Elizabeth Fenna
Sr. Regulatory Project Manager
Regulatory Affairs

99D-2729

C3

AstraZeneca LP
PO Box 4500 Westborough MA 01581-4500
50 Otis Street Westborough MA
Tel 508 366 1100
www.astrazeneca-us.com

Comments on Draft Guidance for Industry "BA and BE Studies for Orally Administered Drug Products – General Considerations"

Section	Comment
Page 2 General Core BA and BE Guidances	We recommend that the guidance "Food Effects Bioavailability and Bioequivalence Studies" be included on this list.
Pages 2, 16, 17 Single Dose vs Multiple Dose Study	The new guideline suggests a shift of focus from absorption values to measures of systemic exposure. However, it is also recommended to use single dose studies instead of steady-state studies because the former ones are more sensitive in detecting differences in absorption rate. These two new recommendations are contradictory and more congruent guides should be provided. The most relevant characteristic regarding systemic exposure for drugs that are given according to multiple dose regimens are parameters obtained in steady-state studies, especially if the pharmacokinetics are non-linear. Furthermore, AUC estimates after single dose administration will be less reliable, due to the need for extrapolation to infinite time. AUC during a dosage interval at steady state should therefore be an option for drugs with long elimination half-lives and/or extended-release products. In these cases excessive blood collection may be needed for calculation of $\geq$80% of the total AUC. The possibility to do steady state studies should therefore at least remain as a clear option for the sponsor.
Pages 9, 13, 17 Early Exposure Metrics	AUC from time zero to tmax will be highly variable due to the, oftentimes, large variability in tmax and will thereby be a very insensitive variable. This will be especially pronounced for Extended Release formulations with zero order release kinetics for which the tmax may vary between 0 and 24 h due to the very even plasma concentration-time profiles. The partial area to tmax should therefore not be a primary variable, but rather be based on drug-specific clinical justifications also for Modified Release formulations (cfr Immediate Release formulations).

Page 13-14 Biowaivers	Chapter V.C.3 outlines the possibilities to obtain a biowaiver pre- (a) and post-approval (b). Pre-approval biowaivers are only accessible in case of new strengths under certain pharmaceutical conditions according to this proposal whereas post-approval, several other possibilities are outlined in the SUPAC guideline. It is suggested that the SUPAC IR guidelines, regarding change of composition and manufacturing changes, could also be applied pre-approval.
P 13, C. Immediate-Release Products: Capsules and Tablets, 1. General Recommendations & p16-17, D. Modified-Release Products, 2.ANDAs: BE studies	It is stated 'BE limit of 90-111% for AUC' for drug products containing a narrow therapeutic range drug or a nonlinear kinetic drug. Is this the established BE criteria for nonlinear kinetic drugs and narrow therapeutic range drugs? Please clarify.
Page 16 Non-linear kinetics	The guidance recommends more narrow goal posts for drugs that exhibit nonlinear kinetics and/or drugs designated as narrow therapeutic range drugs. For the latter case it would probably be justified, but what is the rationale for tighter BE limits in the case of non-linear kinetics? If it is to avoid the fact that small differences during single dose administration will be accentuated/propagated after multiple doses, it would be more relevant to measure the exposure after multiple dosing.
P 17, D. Modified-Release Products, 3. Exposure measurements	Early exposure for Extended Release products does not seem appropriate as a BE measure as the tmax may be very diffuse.

P 18, E. Miscellaneous Dosage Forms	It is stated that chewable tablets should be studied for in vitro dissolution tests under the same conditions as nonchewable tablets of the same active moiety. Should they also fulfill the same acceptance criteria? Please clarify.

TER

his Space

Tracking Label and your address label

ace the Tracking Label to the left of the address label

UPS Shipper Number or place parcel register tape above the address label

UPS Next Day Air
UPS Worldwide Express
Shipping Document

UPS DRIVER
- RECORD 6-DIGIT UPS SHIPPER NUMBER FROM BOX [1].
- IF BOX [1] IS BLANK OR THE NUMBER IS MORE THAN 6 DIGITS, RECORD THE NUMBER FROM BOX [2].

WEIGHT AND ZONE	WEIGHT	DIMENSIONAL WEIGHT	ZONE
	LTR		

NEXT DAY AIR ☐ WORLDWIDE EXPRESS (INTERNATIONAL) ☐ DOCUMENTS ONLY

☐ SATURDAY PICKUP ☐ SATURDAY DELIVERY

SHIPMENT FROM

UPS SHIPPER NO. [1] 015796 [2]

REFERENCE NUMBER

615

TELEPHONE 508-366-1100

LIZ FENNA

ASTRA ~~MERCK~~ ZENECA LP

50 OTIS ST

WESTBOROUGH MA 015813323

DELIVERY TO TELEPHONE

DOCKET NO. 99-23009

FOOD & DRUG ADMINISTRATION

5630 FISHERS LANE, ROOM 1061

ROCKVILLE, MD 20852

0191120 5/98 S

United Parcel Service, Louisville, KY

Letter is to be used for document shipments only.

RESALE FOR INTERNATIONAL SHIPMENTS

N419 055 014 4

N419 055 014 4

N419 055 014 4

DELIVERY 1 EXPORT 2 EXPORT 1

☐ BILL RECEIVER

UPS Next Day Air®
EXTREMELY URGENT

N419 055 014 4

DELIVERY 2

N419 055 014 4
TRACKING NUMBER

DATE OF SHIPMENT 11/1/99

The shipper authorizes UPS to act as forwarding agent for export control and customs purposes. The shipper certifies that these commodities, technology or software were exported from the United States in accordance with the Export Administration Regulations. Diversion contrary to U.S. law is prohibited.

1